Oral Contraceptives and Thromboembolic Disease

THE ASSOCIATION between oral contraceptive use and thromboembolic disease has been known since 1961, at about the same time that these agents came into wide usage in the Western world.[1] The data suggest that oral contraceptives are responsible for about 20 cases of venous thromboembolic disease per 10,000 women users per year.[1] Most commonly these women suffer from superficial or deep vein thrombosis with or without pulmonary emboli. The risk for developing an arterial thrombotic event, such as a myocardial infarct or stroke, appears to be an order of magnitude lower.[1]

In this issue, Schneiderman and Cello report on a rare complication of oral contraceptive use—namely, intestinal ischemia with or without infarction. In all, they found 41 cases of ischemic disease in oral contraceptive users, of whom 15 experienced reversible bowel injury, while 26 suffered frank intestinal necrosis. In this latter group, eight (31%) of the patients died. Considering the fact that about 8 million American women currently use oral contraceptives,[1] it is fortunate that there is such a low risk for this serious disorder.

In one case of transient ischemia, histologic examination of mesenteric tissue showed multiple thrombi in branches of the inferior mesenteric artery. In patients with intestinal infarction, thrombi were commonly observed in either mesenteric arteries or veins. In about 65% of the cases, thrombosis occurred in the venous distribution. The observation that events may be either venous or arterial suggests that the disorder must be explained by several factors rather than one single abnormality. This follows from a large body of literature suggesting that in arterial thrombotic events, deranged platelet physiology is a major factor while in venous disorders, defects in proteinase inhibitors, particularly antithrombin III, or elevated levels of procoagulants appear to play a more important role.[1,2] Oral contraceptive users show numerous alterations in their coagulation system, including hyperaggregable platelets, elevated levels of procoagulants and decreased levels of antithrombin III.

Deranged fibrinolysis also may play a central role in the pathogenesis of thromboembolic events.[2-5] Studies suggest that patients with decreased vascular stores of tissue plasminogen activator (t-PA) are predisposed to venous thromboembolic disease. Whenever a clot forms in the adjacent lumen, t-PA is released from blood vessel walls. In the presence of fibrin as a cofactor, it rapidly activates plasminogen, which will dissolve blood clots by proteolytic digestion of the fibrin. The blood contains vast amounts of plasminogen, but vessel walls possess minimal stores of t-PA and release of this activator is clearly the rate-limiting step in fibrinolysis. Low levels of releasable vascular t-PA are genetically regulated, although factors such as smoking and exercise modulate release of this protein.[2,6]

The interrelationship of t-PA and estrogens is complex. With oral contraceptive use, t-PA levels are somewhat suppressed, and this effect may play a role in thromboembolic disease.[1,2] However, this does not appear to be a major factor in the pathogenesis of thrombosis in these women. Groups of women with a history of thromboembolic disease while using oral contraceptives have been studied. About 90% of such patients show releasable t-PA levels at least 25-fold less than normal.[2,4,5] None of these subjects used oral contraceptives for at least a year before study. Since estrogens show no residual effect on coagulation after three months of withdrawal,[1] it must be concluded that diminished vascular t-PA stores are a predisposing factor in thromboembolic disease. Most of the data indicate a strong relationship between t-PA and *venous* thromboembolic disease.[2-5] In all these reports, only six women with *arterial* thrombosis were available for study, and these women did not have low levels of vascular t-PA.[5] This is a small number of subjects, however, and probably cannot be viewed as a statistically significant sample. Other studies do suggest an association between low levels of vascular t-PA stores and myocardial infarcts[7] or strokes,[8] although neither study involved oral contraceptive users.

Recently, our laboratory has studied patients with a relatively rare disorder, atrophie blanche.[9] These persons present with recurrent skin ulceration and fibrosis. The disease appears to result from a cutaneous vasculitis, and thrombi are found in the microcirculation, including arterioles and small arteries. These patients show levels of releasable t-PA more than 25-fold less than normal, which further supports the notion that arterial thromboembolic disease may be related to low levels of vascular t-PA stores. Subsequently, we have studied a group of about 30 patients with various other forms of vasculitis (J. Jordan, MD, S.V. Pizzo, MD, PhD, unpublished data, June 1986). Here, too, we observed that patients with active disease had low levels of releasable vascular t-PA (about 20-fold less than normal).

These data suggest a model for thrombosis in women taking oral contraceptives. A number of changes develop in their coagulation system. In some, platelet alterations may predominate while in other women changes in levels of procoagulants are paramount. Depending on the extent of derangement of the hemostatic system, thrombosis will be triggered in some of these women. Most typically, a venous thromboembolic event will occur, but in a small percentage of women, arterial thrombosis results. At this point, the most important factors are a patient's defense mechanisms against clot propagation. These defense mechanisms include levels of antithrombin III and vascular stores of t-PA. In some women on an oral contraceptive regimen, antithrombin III levels may fall significantly, perhaps by as much as 20%.[2] If, in addition, a woman has inadequate stores of vascular t-PA for any of the reasons described above, she is now at high risk for a thrombotic event and for overt disease to develop. It must be emphasized that alterations in antithrombin III induced by the pill, or the predisposition to release less than normal levels of vascular t-PA, represent alterations that would not be significant unless a coagulation event has occurred since these proteins play no role in the initial thrombotic event. Hence, the hypercoagulable state in oral contraceptive users is complex and involves derangement of the coagulation system and one of its prime inhibitors in a setting of defective fibrinolysis.

While it is possible to present a model for oral contraceptive-associated thromboembolic disease, it is important to understand the limits of such a hypothesis. In theory, one might suggest a strategy for identifying women at high risk for thrombosis to develop while taking the pill. This approach would consist of measuring t-PA levels before women begin taking oral contraceptives and then measuring antithrombin

III, t-PA and procoagulant levels several months later. The problem with this approach is that hundreds of women per 10,000 users will show significant alterations in the hemostatic balance, but in only about 20 of them each year will a thromboembolic event develop. It would appear that the cost/benefit ratio would not favor such an expensive approach, which is likely to have a high false-positive index.

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It Could Be an Important First Step

AT ITS MEETING in June of this year the House of Delegates of the American Medical Association (AMA) adopted report MM of the Board of Trustees. This could prove to be an important action by the AMA. The report is the result of a careful study by the Council on Medical Service, the Council on Legislation and the Board of Trustees. It is a thoughtful proposal for financing (or refinancing) the health care of the elderly in this nation. It addresses a number of problems that must be dealt with realistically if the Medicare program is not to face almost certain fiscal and perhaps even political disaster in the years ahead.

The AMA proposal would eliminate the current Medicare program but honor the commitments already made to the elderly. To this writer the specifics of the plan are not as important as are some of the principles it embodies. It restores the original purpose of Medicare, which was to provide access to affordable high quality health care for the elderly, and to this end it would remove care for the disabled (unless elderly) and the care of end stage renal disease (ESRD) from the program except for the elderly. These needs would then be financed from some other source.

Another basic concept of the AMA proposal is that Medicare be self-funded, but in a new way. At present about four workers are taxed to support the health care of one Medicare recipient. By the middle of the next century demographic change will reduce this to only two workers, likely to be a politically unacceptable arrangement. And it has been estimated that the present program will be 1 trillion dollars in debt by the year 2010, likely to be an economically unacceptable arrangement. The AMA proposal wisely envisions a new approach. Over time, that is before the middle of the next century, the present intergenerational transfer of resources from earners to Medicare beneficiaries will be replaced by a program prefunded by the potential beneficiaries themselves through tax contributions during their own working years. This would be augmented by voluntary health individual retirement accounts (HIRAs) which would be tax free if used to cover supplemental health care expenses. The proposal would also create a new semiautonomous federal agency to administer the program. This would be somewhat on the model of the Federal Reserve Board to give it a modicum of political independence. Other provisions would take advantage of the resources of the private sector to provide the health care, and would require some reasonable fiscal participation by the beneficiaries based on their ability to pay as determined by their annual incomes. Conspicuously absent from the proposal, which otherwise seems quite comprehensive and well thought out, is any mention of utilization review or cost control. It would seem that these will be as important in any new program as they have been found to be in the program as we know it now. But the report makes no claim to be complete or final. It is only being presented at this time with the hope that it will stimulate discussion and debate, and indeed it should.

The AMA is surely to be commended for developing this imaginative and innovative proposal. It seems in many ways to be right on target. It can be viewed as affirmative action in behalf of patients and the public. One can hope that discussions with other interested parties will develop, and that in time all those with interests at stake will become involved. One can also hope that as this occurs, and some sort of agreement or consensus is reached, an effective coalition of various groups and parties at interest will come into being and thus provide the energy and resources necessary to bring about the change that by then they all will have recognized as needed and desirable. Experience would suggest that it is unlikely that the physicians of America and the AMA can do all this alone, but the proposal adopted by the House of Delegates could be an important first step. The AMA plans to encourage wide discussion of the proposal and the problems it seeks to solve, and let us all hope that this occurs.

MSMW

Pheochromocytoma

THERE is no more important and treacherous cause of hypertension to recognize and treat appropriately than pheochromocytoma since the tumor can be successfully removed in 90% of patients. If unrecognized, it will usually cause a catastrophic cardiovascular event or death. Therefore, even though pheochromocytoma is a rare cause of hypertension (probably occurring in less than 0.1% of the population with diastolic hypertension), it is extremely desirable to repeatedly expose and sensitize clinicians to the vagaries of this most exciting and fascinating "pharmacologic bomb"—a tumor whose clinical expression, often dramatic and explosive, has rightly earned it the title of "the Great Mimic."

The clinicopathologic conference in this issue is a highly valuable exercise (as were two cases of pheochromocytoma recently reported as clinicopathologic exercises in the *New England Journal of Medicine,* Case 9-1985 [1985; 312: 568-575] and Case 6-1986 [1986; 314:431-439]). Dr Rutledge's admirable discussion of the differential diagnosis and